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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/582,391	KISS, ZOLTAN	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/21/2007;12/29/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-9 and 11-21 are pending in this action. Claims 10 and 22-116 have been cancelled

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on 8/21/07 and 12/29/06 are acknowledged and have been reviewed.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 13-20 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus

because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may also be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

The claimed invention is drawn to a method of administering to a mammal a therapeutically effective amount of an inhibitor of α_1-antitrypsin inhibitor. The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the very broad genus comprising α_1-antitrypsin inhibitor (see instant specification page 9, lines 12-15). The specification and claims do not describe elements which are essential to the genus comprising such α_1-antitrypsin inhibitor.

Thus, the scope of the claims includes numerous structural variants, and the genus is highly variable because a significant number of structural differences between members of the genus is permitted. Concise structural features that could distinguish structures or compounds within this genus from others are missing from the instant disclosure. The specification fails to teach or adequately describe a representative number of species in this broad genus such that the common attributes or characteristics concisely identifying members of the genus are exemplified, and, because the claimed genus is so highly variable, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed. Thus, Applicant was not in possession of the claimed genus.

4. Claims 8 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus

because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may also be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if

the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

Applicant has not provided a description of the structure of a representative number of compounds nor a description of the chemical and/or physical characteristics of a representative number of compounds nor a description of how to obtain a representative number of an "active derivative" thereof as recited in the instant claim 8.

In other words, the Applicant has not described with sufficient clarity what the active derivative thereof derivatives thereof for gemfibrozil and or lithocholic acid as claimed. For example instant specification (see page 11, lines 16-20) only defines derivatives as '"active derivative" is used to refer to a derivative or substitute for the stated chemical species that operates in a similar manner to produce the intended effect, and is structurally similar and physiologically compatible".

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6, 8, 12, 14-15 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Ridker et al. (WO 2002/48715).

Ridker et al. disclose the use of diagnostic test to identify patients with high or elevated levels of C-reactive Protein (CRP) or interleukin-6 in humans (women) that

may benefit from the administration of a lipid lowering agent (i.e., α_1-antitrypsin - gemfibrozil) (as it relates to instant claims 1, 3, 6, 8 and 21; see page 2, line 16-24, page 3, lines 12-18, page 11, line 26).

Ridker et al. further disclose that the step of identifying includes an immunoassay of the blood (see page 18, lines 1-5; as it relates to instant claim 2). Additionally Ridker also discloses the treatment or lowering the risk of diabetes in a patient may include co-administration of other anti-diabetic drugs such as insulin for synergistic or additive treatment effect (see page 23, lines 21-25; as it relates to claims 14 and 15). Therefore, it is inherent that gemfibrozil is administered at that dosage because of the specific teaching that lipid lowering agents are used for treating or reducing the risk of diabetes once a day (as it relates to claim12; see page 20, lines 31-34).

With regard to claims 4 and 5 wherein the blood glucose level is maintained at 10 mm or between 4 and 6 mm is an inherent property of the administration of the inhibitor of α-antitrypsin. The claims do not recite additional steps or products to be administered, but rather recite effects which will necessarily occur upon performing the method of instant claims 1 and 3. Once the drug is administered in a therapeutically effective amount the characteristics of the drug in maintaining the blood glucose level below 10 mm and between 4-6 mm will be achieved.

6. (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 8, 12, 14-15, and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Ridker et al. (US 2003/0100486).

Ridker et al. disclose a method of treating or lowering the risk of diabetes in an individual by screening the individuals (i.e., humans) for high or elevated levels of C-reactive Protein (CRP) or interleukin-6 in human that may benefit from the administration of a lipid lowering agent (i.e., α_1-antitrypsin-gemfibrozil) (as it relates to instant claims 1, 3, 6, 8 and 21; see ¶'s 0003, 0009, 0013-0014, 0038 and 0043).

Ridker et al. further disclose that the step of identifying which includes an immunoassay of the blood (see ¶ 0057; as it relates to instant claim 2). Additionally Ridker also discloses that the treatment or lowering the risk of diabetes in a patient may include co-administration of other anti-diabetic drugs such as insulin for synergistic or additive treatment effect (see ¶ 0077; as it relates to claims 14 and 15). Therefore, it is inherent that gemfibrozil is administered at that dosage because of the specific teaching that lipid lowering agents are used for treating or reducing the risk of diabetes once a day (as it relates to claim 12; see ¶ 0066).

With regard to claims 4 and 5 wherein the blood glucose level is maintained at 10 mm or between 4 and 6 mm is an inherent property of the administration of the inhibitor of α-antitrypsin. The claims do not recite additional steps or products to be administered, but rather recite effects which will necessarily occur upon performing the method of instant claims 1 and 3. Once the drug is administered in a therapeutically effective amount the characteristics of the drug in maintaining the blood glucose level below 10 mm and between 4-6 mm will be achieved.

Applicant should note that "claiming same invention" means either the exact same invention (like a 102) or an obvious variant (like 103). See MPEP 715.05, last two paragraphs (see MPEP 706.02(b) and 715.05) cannot be overcome by a declaration under 37 CFR 1.131. Claim 37 of Ridker et al claims a lipid lowering agent (as defined a lipid lowering agent is gemfibrozil) by determining the specific marker levels of systemic inflammation (see claims 22-24 of Ridker).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-9, 11-12, 14-15 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ridker[1] et al. (WO 2002/48715) and/ or Ridker[2] et al. (US 2003/0100486) in view of Ganrot et al. Acta Endocrinologica (1976) vol. 55 p 537-544. Ridker[1,2] et al. is applied here as above (1 and 2) see ¶'s 6 and 7 above. Ridker et al. disclose generally that doses of the active compounds are from 0.1-1000 mg/kg/day.

However, Ridker[1,2] et al. fail to teach the gemfibrozil is adjusted daily to maintain a normal blood level of α_1-antitrypsin (as required by instant claim 11) nor do they teach the inflammation marker protein is antitrypsin, wherein the above-normal blood level is greater than 1.3 mg α_1-antitrypsin/mL blood. Ridker also fails to teach the specific dosage range of gemfibrozil to be 300-1500 mg per day as required by instant claim 9. Ganrot is introduced for its teaching of determining the inflammation marker protein α_1-antitrypsin blood level in patients with diabetes (see abstract, as it relates to claim 7) wherein the patients showed significant increase of α_1-antitrypsin (see Table 1 and p 542 under α_1-antitrypsin). Intrinsically the blood serum level of α_1-antitrypsin is above 1.3 mg/L blood, because Ganrot specifically teach a significant increase of α_1-antitrypsin level. Thus indicative of above normal values above 1.3 mg/L.
However, Ganrot fails to teach administering an inhibitor of α_1-antitrypsin.
It would have been obvious to one of ordinary skill in the art to monitor the blood level of the markers such as inhibitor of α_1-antitrypsin because α_1-antitrypsin deficiency is a disease caused by reduced or abnormal production in the body of the enzyme inhibitor α_1-antitrypsin and shows the at risk factor of developing hyperglycemia. Therefore monitoring the levels in a patient taking an anti-diabetic drug such as gemfibrozil would

have been obvious as this is a normal procedure for diabetes due to several underling features such as diet, exercise etc., in order to deliver the appropriate insulin produced by the liver absent factual evidence to the contrary.

Even though Ridker fails to teach instant claim 9, Although Ridker fails to teach the specific dosage range required in instant claim 9, Ridker teaches that generally doses of the active compounds are from 0.1-1000 mg/kg/day and the preferred dose is from 50-500 mg/kg/day. Therefore, one of ordinary skill in the art would be motivated to determine the optimum dosage range because the determination of a dosage having the optimum therapeutic index is well within the level of the ordinary skill in the art, and the artisan would be motivated to determine the optimum amounts to get the maximum effect of the drug, hence the reference makes obvious the instant invention (as required by instant claim 9).

8. Claims 1, 13, 14, 16-17 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ridker[1] et al. (WO 2002/48715) and/ or Ridker[2] et al. (US 2003/0100486) in view of Ridker et al. (US 6,040,147) and Kidrom et al. (US 4,579,730) and further in view of Kiss (2004/0120940) as evidence by Festa et al. (Diabetic Medicine, (2002),19(11): 939-943.

Ridker[1,2] et al. are applied here as in ¶'s 6 and 7 above (as it relates to claims 1 and 14).

However, Ridker[1,2] et al. fail to teach the co-administration of the requirements by claims 13 and 16-20. Nonetheless, Ridker[1,2] et al teach agents such as cyclogenase-

2 inhibitor, anti-inflammatory agents or first generation sulfonylureas (insulin secretogogue) may be used to lower the risk of diabetes (see ¶ 0020) and further teaches that co-administration of other agents for reducing the risk of diabetes.

Therefore these prior arts are introduced.

The '147 patent teaches predicting future risk of atherosclerosis, a known diabetes complication, by detecting CRP values in blood at levels about 0.60mg/dl (See figure 2, in particular, as required by claim 1), in addition the '147 patent teaches evaluating the likelihood that an individual will respond from treatment with an anti-inflammatory agent, lipid lowering agent or COX-2 inhibitor (i.e. aspirin also a non-steroidal anti-inflammatory drug, as required by instant claim 20) by measuring CRP in blood an obtaining values of 0.60 mg/dl or above.

However, '147 fails to teach co administration with an alpha-antitrypsin inhibitor or other drugs.

Kidrom et al. teaches a composition for oral administration of insulin comprising an insulin and a bile acid agent lithocholic acid for promotion of the absorption of insulin (see abstract and col. 2, lines 20-25, as required by instant claims 1 and 13) to have the same effect as naturally secreted insulin on the blood glucose level.

However, Kidrom fails to teach co-administration with other antidiabetic agents, nor does Kidrom teaches the method of delaying diabetes or identifying the mammal with an above normal blood level of an inflammatory marker.

Kiss teaches the use of human placental alkaline phosphatase to reduce blood glucose level in a mammal, which intrinsically will delay the progression of onset

diabetes (as recited in instant claims 1, 17 and 21, see abstract). Kiss further teaches controlling hyperglycemia is accomplished by the administration of several medications in five major groups daily (i.e., insulin secretogogue, biguanides, inhibitors of alpha glucosidase, thiazolidinediones and insulin (see ¶'s 0011-0015). Therefore the limitations of claims 15-16 are met.

However, Kiss fails or is silent in teaching identifying the mammal with an above normal blood marker protein. None the less before practicing Kiss teaching the mammal with an above normal blood level would have been identified by method known to one of ordinary skill in the art.

One of ordinary skill in the art would have been motivated to identify the mammal with an above–normal blood level of an inflammatory marker protein because knowing the level of the inflammatory marker in a patient with above normal level inflammatory marker protein might benefit from treatment regimen that may lower the risk of developing diabetes or other diseases related to above normal level of the marker. Therefore one of ordinary skill in the art would treat the mammal based upon the net benefit to the patient.

Based on the patient's result and diagnoses, one of ordinary skill in the art would be motivated to combine a NSAID (such as those disclosed by Ridker[1,2] et al and '147) or an insulin secretogogue to a lipid inhibiting agent such as gemfibrozil for a synergistic effect in reducing the mammal's blood level and further decrease any other complication related to the above-normal level of CRP for example.

As evidence by Festa et al. chronic, subclinical inflammation, as indicated by elevated circulating CRP levels, is more strongly associated with post-challenge glycaemia than with fasting glucose levels in non-diabetic subjects (see entire disclosure of Festa). This association is partially independent of body fat and insulin resistance. Therefore one of ordinary skill in the art would have been motivated to reduce the progression of diabetes by the administration of lithocholic acid.

Also based on the teaching of Kiss one of ordinary skill in the art would have been motivated to add an anti-diabetic agent such as human placental alkaline phosphatase (hPALP) to the treatment of Ridker[1,2] et al and '147 because hPALP as taught by Kiss has a powerful insulin-independent stimulatory effects on glucose uptake.

In summary it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to measure serum CRP levels for uses such as characterizing the risk profile of patient for developing diabetes in an apparently healthy individual or evaluating the likelihood that an individual will benefit from treatment, given CRP's known association with type I diabetes, as taught by Ridker et al. supra given that it is well known to measure a known marker for the presence of, or predisposition to, diabetes.

9. No claim is allowed

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. V. G./
Examiner, Art Unit 1618
8/7/09

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618